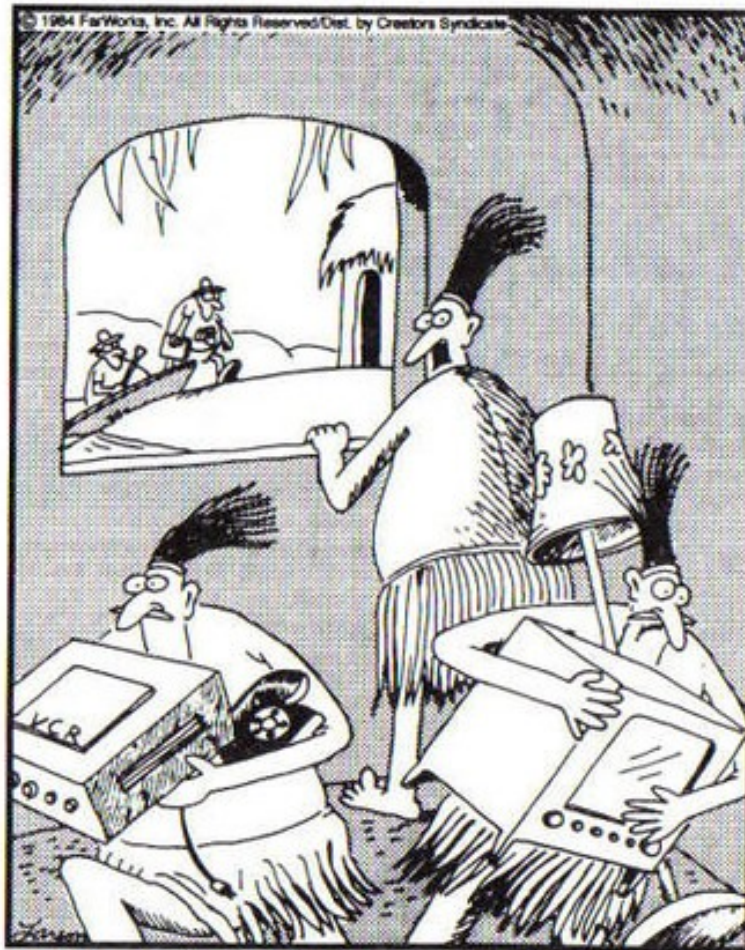


# THE FAR SIDE® BY GARY LARSON



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"Anthropologists! Anthropologists!"

**Let food be your  
medicine  
and medicine be your  
food.**

- Hippocrates, 400 BCE**

“One future intelligence problem:  
knowing what drugs the other guys  
are on.”

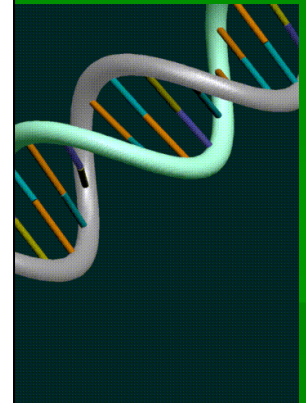


# SAME SPECIES...VERY DIFFERENT CREATURES

Nurture

AND

Nature



# Assumptions

- Common dietary compounds act on the human genome, directly or indirectly, to alter gene expression or structure;
- Some individuals, under some circumstances, can have diet become a serious risk factor;
- Some diet-regulated genes and their normal common variants help shape processes like susceptibility to disease/injury/extreme environments and progression, recovery from, and severity of breakdown
- The degree to which diet influences these processes depends in part on an individual's genetic makeup
- Dietary interventions based on the “nutriome” can be used to prevent, mitigate, or cure disease/injury<sup>1</sup>

■ Kaput and Rodriguez, 2004 “Nutritional Genomics”,  
*Physiol Genomics* 16(2):166-167

<sup>1</sup>...and possibly, gasp, enhance performance



# What this briefing is NOT about

- Thorough literature review

GKMM Ncol

PPAR $\alpha$  G/C

ACE I/D

ADRA2A

ACTN3  
R577X

NO  
Glu289ASp  
ADRB2

APOE

Spl transcr

- List of Single

Items 1 - 20 of 198

- 1: [Steiner C, Arnould S, Scalbert A, Manach C.](#)  
Isoflavones and the prevention of breast and prostate cancer: new perspectives opened by nutrigenomics.  
Br J Nutr. 2008 May;99 E Suppl 1:ES78-108.  
PMID: 18303737 [PubMed - in process]
- 2: [Ovesná J, Slaby O, Toussaint O, Kodicek M, Marsik P, Pouchová V, Vaněk T.](#)  
High throughput 'omics' approaches to assess the effects of phytochemicals in human health studies.  
Br J Nutr. 2008 May;99 E Suppl 1:ES127-34.  
PMID: 18303733 [PubMed - in process]
- 3: [Mortensen A, Sorensen IK, Wilde C, Dragoni S, Mullerová D, Toussaint O, Zloch Z, Sgaragli G, Ovesná J.](#)  
Biological models for phytochemical research: from cell to human organism.  
Br J Nutr. 2008 May;99 E Suppl 1:ES118-26.  
PMID: 18303732 [PubMed - in process]
- 4: [Stienstra R, Duval C, Keshkar S, van der Laak J, Kersten S, Müller M.](#)  
PPARgamma activation promotes infiltration of alternatively activated macrophages into adipose tissue.  
J Biol Chem. 2008 Jun 9. [Epub ahead of print]  
PMID: 18541527 [PubMed - as supplied by publisher]
- 5: [Sáiz J, Cabrer JM, Rosselló CA, Palou A, Picó C.](#)  
Formation of human obnoxious products of acrylamide after its ingestion in rats in dependence on age and sex.  
J Agric Food Chem. 2008 Jul 5;56(13):4096-101. Epub 2008 Jun 10.  
PMID: 18540624 [PubMed - in process]
- 6: [Caramia G.](#)  
Omega-3: from cod-liver oil to nutrigenomics.  
Minerva Pediatr. 2008 Aug;60(4):443-455.  
PMID: 18511896 [PubMed - as supplied by publisher]
- 7: [Martinez JA, Parra MD, Sandoval M, Moreno-Aliaga MJ, Martí A, Martínez-González MA.](#)  
Genotype-dependent response to energy-restricted diets in obese subjects: towards personalized nutrition.  
Asia Pac J Clin Nutr. 2008;17 Suppl 1:119-22. Review.  
PMID: 18296317 [PubMed - indexed for MEDLINE]
- 8: [Lee YY, Tsou CS, Lin HC, Jen CH, Wu YT.](#)  
Global perspective of health related edible plants from the agricultural point of view.  
Asia Pac J Clin Nutr. 2008;17 Suppl 1:95-8. Review.  
PMID: 18296311 [PubMed - indexed for MEDLINE]
- 9: [Kato H.](#)  
Nutrigenomics: the cutting edge and Asian perspectives.  
Asia Pac J Clin Nutr. 2008;17 Suppl 1:12-5. Review.  
PMID: 18296291 [PubMed - indexed for MEDLINE]

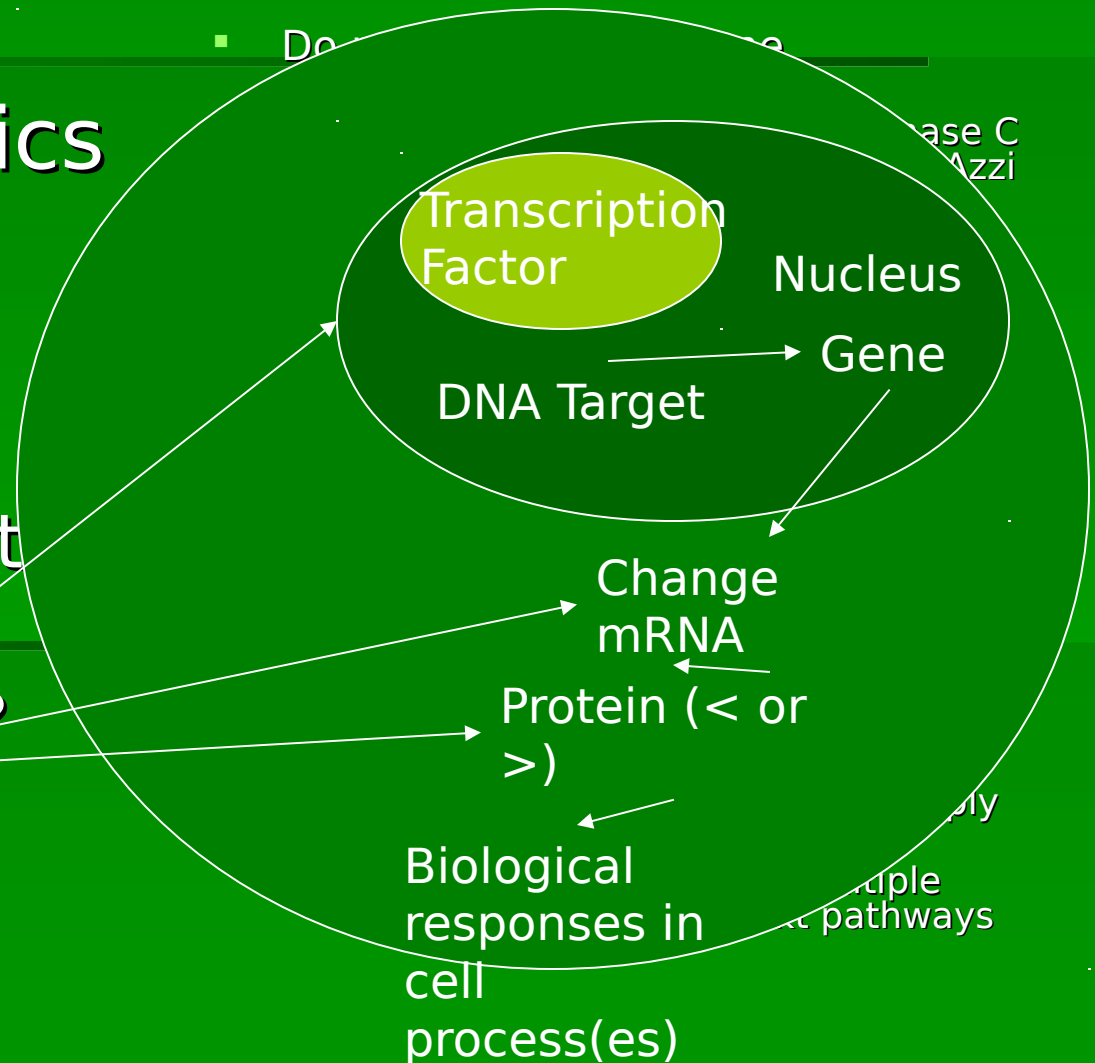
(-/-)

# Nutrigenomics (Nurture)

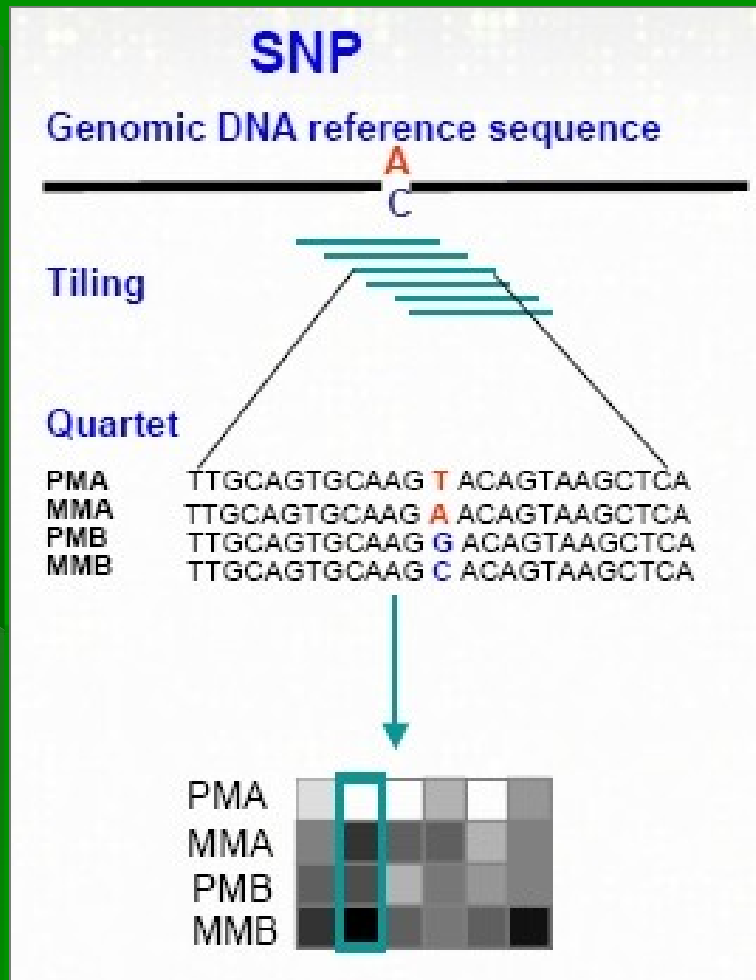
- Nutrigenomics

- Nutrition + genomics
- How do nutrients alter gene expression?

Essential and non-essential nutrients



# Nutrigenetics (Nature)

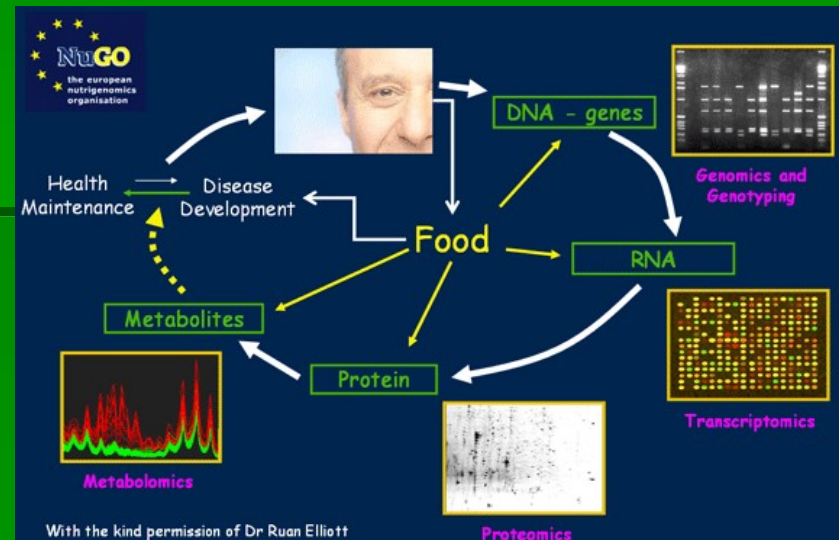


- SNPs occur once every 1k to 2k nucleotides, but occur at a frequency > 1% in the population
- Effects can be variable and not always dramatic
  - Can alter protein structure and function when the nucleotide base substitution occurs in a gene's coding region
  - When substitution occurs as part of the gene's regulatory promoter, the SNP may affect the conditions under which the protein is made



# Omics: you can't stop with just one

- Nutrigenomics
- Epigenomics
- Nutritional epigenomics (as they influence DNA methylation, histone modification, and RNA-associated silencing)
- Transcriptomics
- Proteomics
- Metabolomics
- Microbiomics
- Connectomics
- HPomics



The figure consists of two photographs of a female figurehead and a line graph. The figureheads show a transition from a female appearance (left) to a male appearance (right) after testosterone treatment. The graph plots the T/E ratio (Testosterone to Estrone ratio) on the y-axis (0 to 150) against the number of days after the testosterone dose on the x-axis (0 to 15). Three genotypes are compared: ins/ins (solid squares, dotted line), ins/del (open triangles, dashed line), and del/del (solid circles, solid line). The ins/ins group shows the highest T/E ratio, peaking around day 7. The ins/del group shows a moderate increase. The del/del group remains near the baseline, which is highlighted by an orange oval.

Days after testosterone dose	ins/ins (T/E ratio)	ins/del (T/E ratio)	del/del (T/E ratio)
0	~5	~5	~5
1	~25	~10	~5
3	~80	~30	~5
5	~85	~45	~5
7	~95	~50	~5
9	~75	~45	~5
11	~65	~40	~5
13	~55	~35	~5
15	~45	~30	~5



1997

Van Dongen, H.

P. A., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *SLEEP*, 26, 117-126.

- 2007 Apr 17; 16(2):1-10. Epub 2007 Mar 8.

her SN, James LM, Grouff C, LeC, Stone DJ, Nor, Feldman C, Collins S

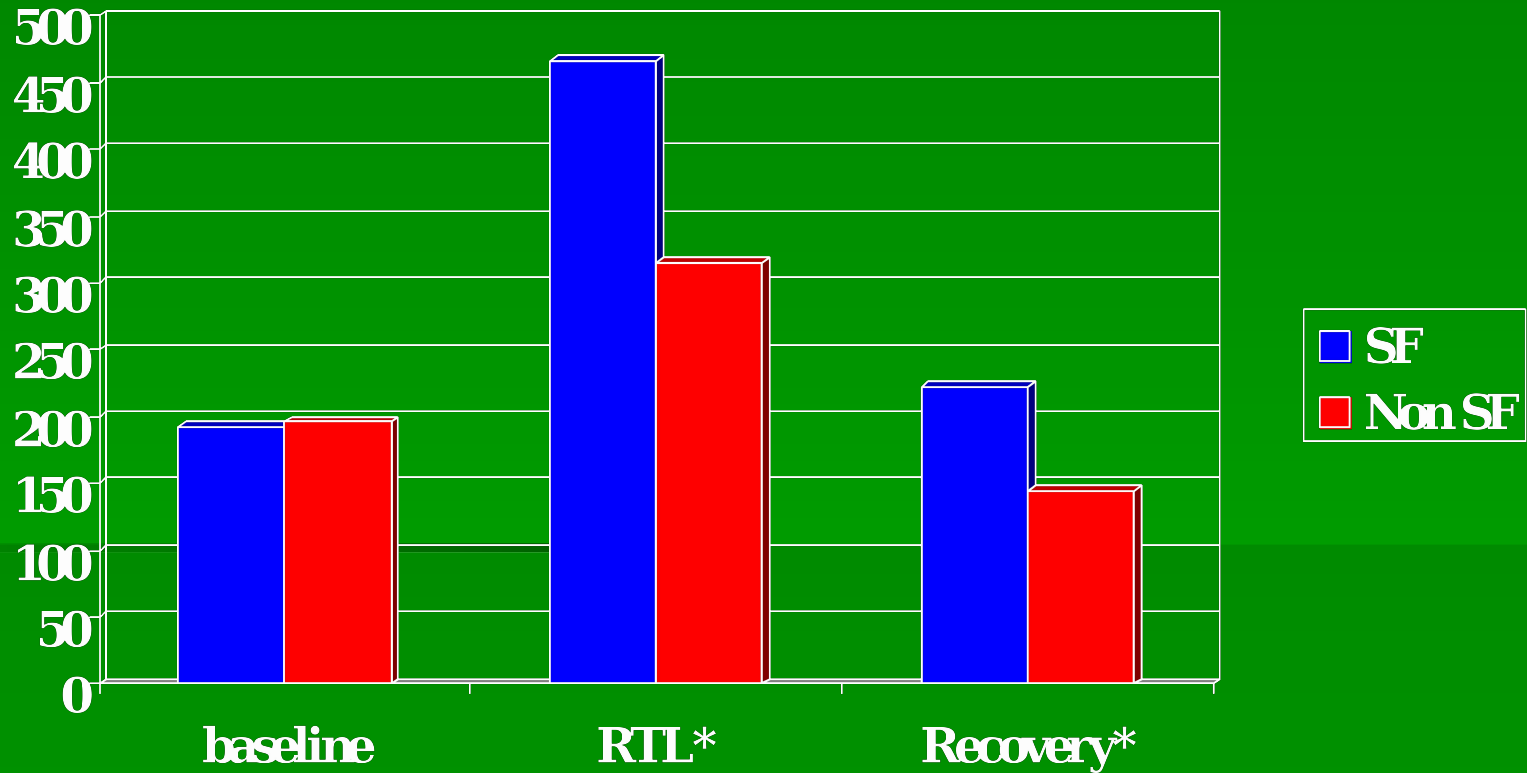
a Korean Asian than in a Swedish Caucasian population, with 66.7 and 9.3 % deletion/deletion (*del/del*) homozygotes respectively.

Jakobsson J et al. "Doping Test Results Dependent on Genotype of UGT2B17, the Major Enzyme for Testosterone Glucuronidation." *J Clin Endocrin Metab.* March 11, 2008

# **Nutrigenomics: speculation**

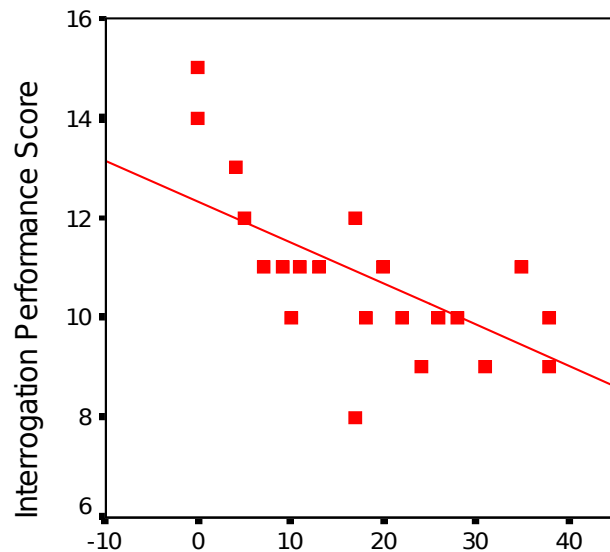
# Neuropeptide Y

(Morgan et al., 2000; 2001)



# NPY and Human Performance: best and non-performers

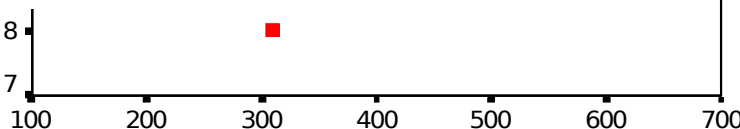
Dissociation and Performance



Dissociation Score (CADSS)

$r = -.68; p < 0.0001$

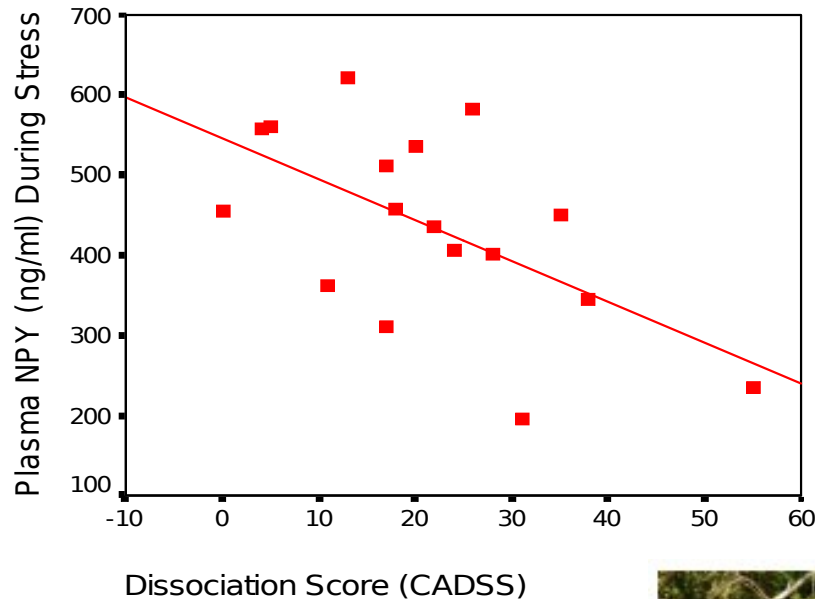
Perfor



Plasma NPY (ng/ml) during stress exposure

$r = .49; p < 0.02$

NPY and Dissociation



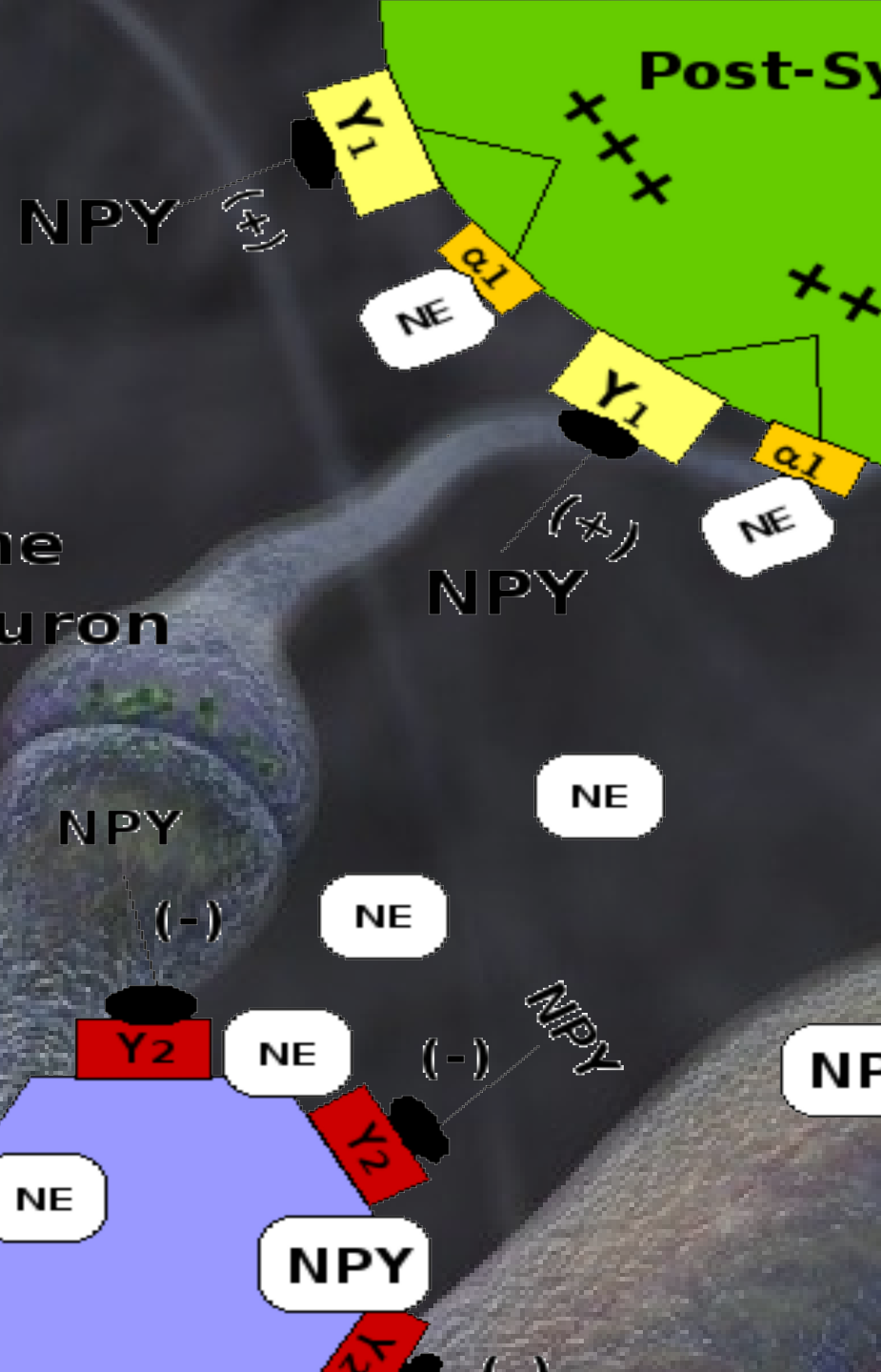
$r = -.58; p < 0.01$

$Rsq = 0.3390$

$Rsq = 0.2044$



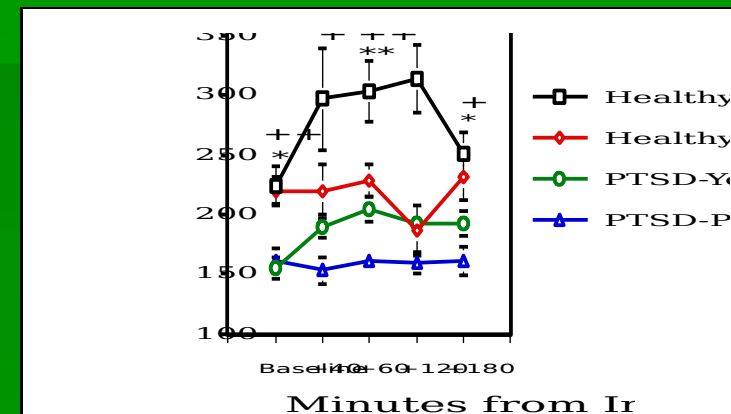
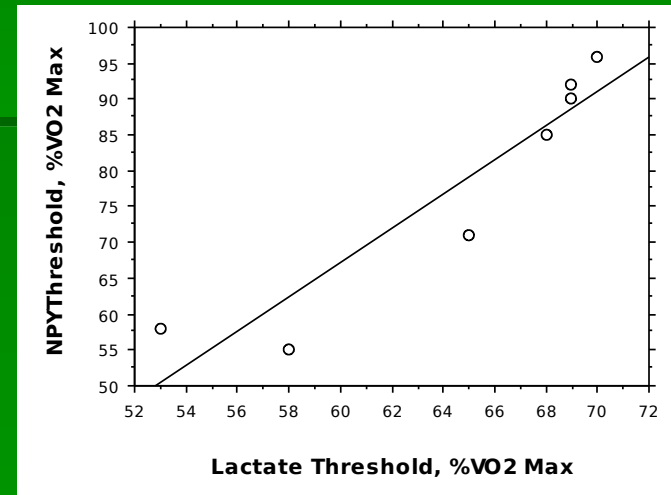
# NPY Potentiates Effects of NE at the Post-Synaptic Neuron Via Y1 Receptors





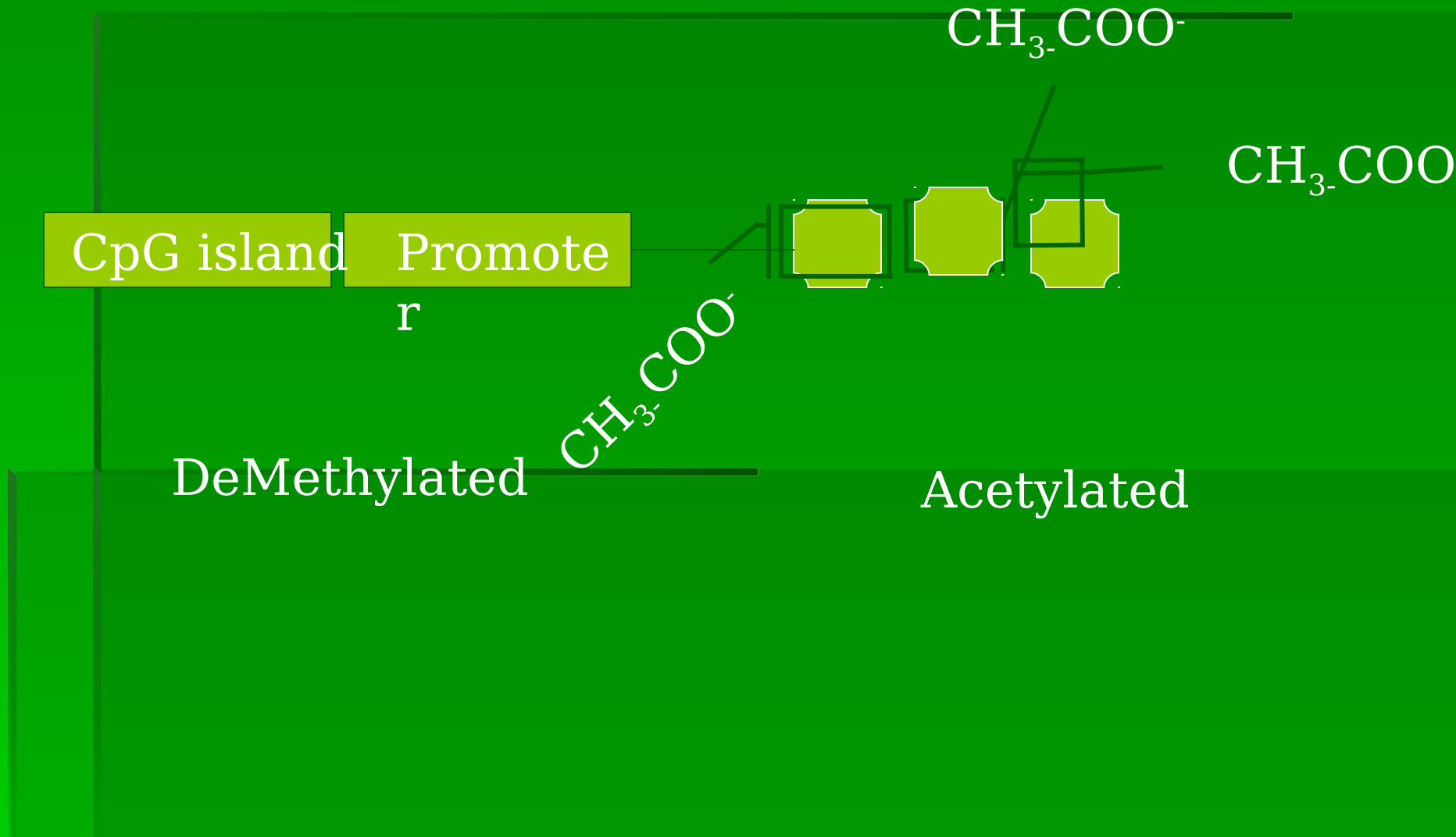
# Clinical NPY Data

- Increased NPY found in response to 75% VO<sub>2</sub> max exercise (Lundberg 1985), the cold pressor test (Morris 1986), and in response to noradrenergic activation by alpha-2 receptor antagonist yohimbine (Rasmusson 1998)
- Reduced NPY noted in CSF of patients suffering from major depression (Widerlov 1992), suicide victims (Widdowson 1992) Negative correlation noted between anxiety scores and CSF NPY levels in patients with depression (Heilig 1990)
- Reduced baseline NPY & blunted NPY response to yohimbine stimulation in veterans with PTSD (Rasmusson 2000).



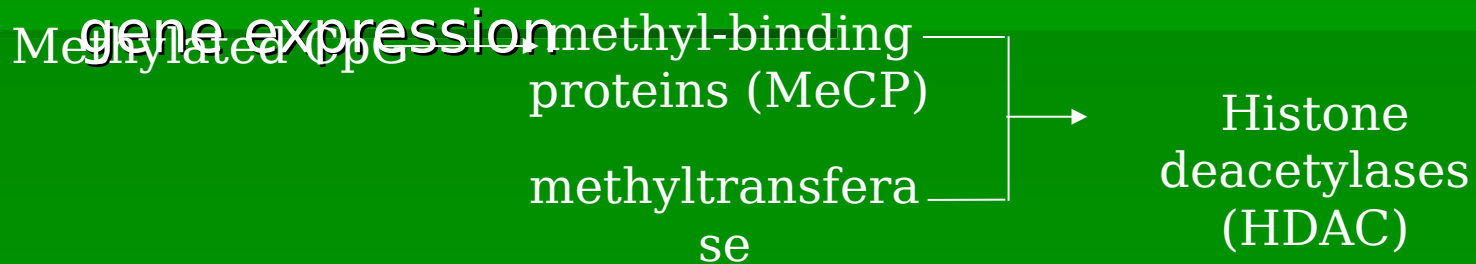
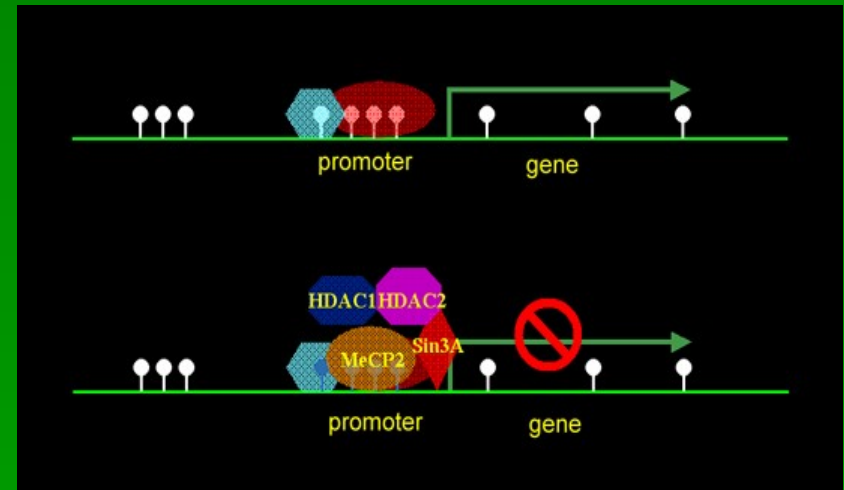
# Epigenetic Regulation

## “Active Gene”



# Epigenetics

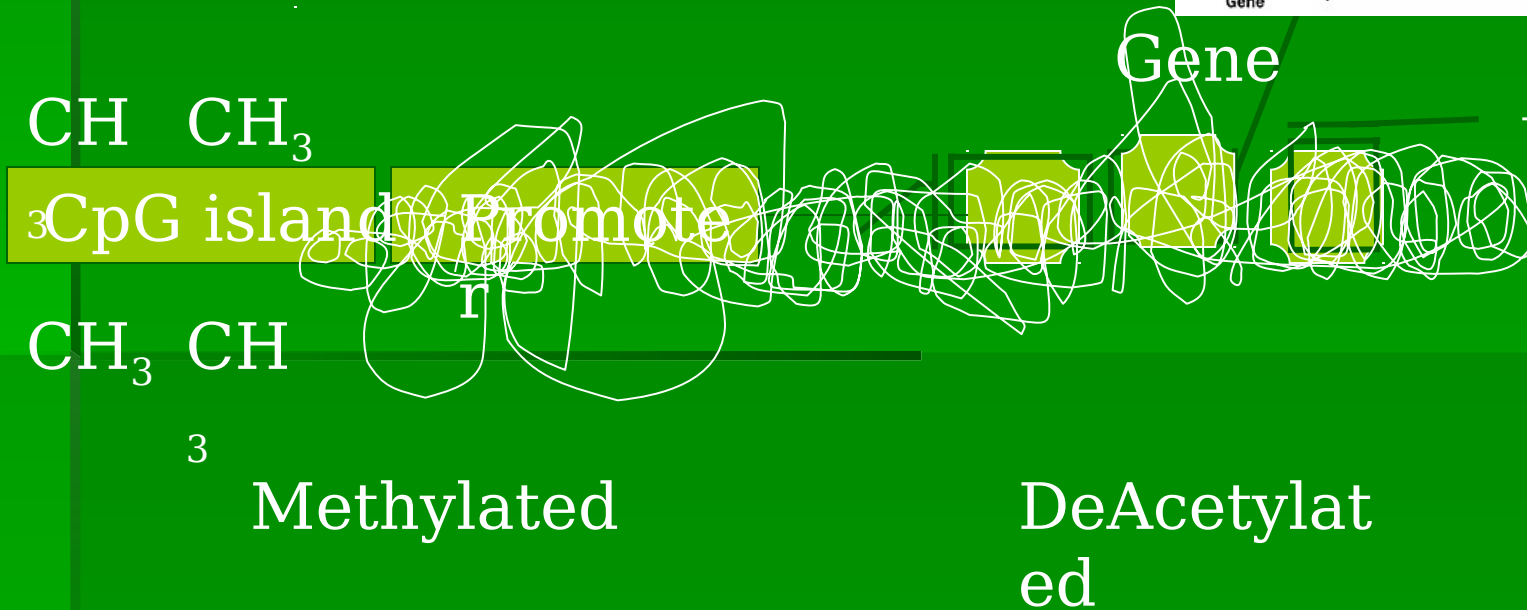
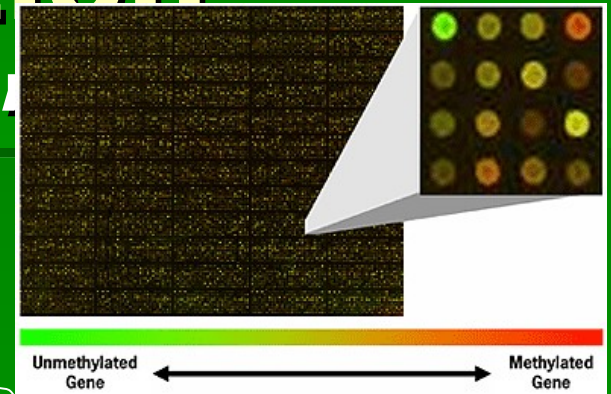
- Promoters are regulatory elements upstream the 5' end of TSS.
- Methylation of promoter CpGs remodels the chromatin structure for



"Pattern Detection and Co-methylation Analysis of Epigenetic Features in Human Embryonic Stem Cells." 2008 Presentation by Ben Niu, Qiang Yang, Jinyan Li, Hong Xue, Simon Chi-keung Shiu, Weichuan Yu, Huiqing Liu, Sankar Kumar Pal.  
Hong Kong Polytechnic University

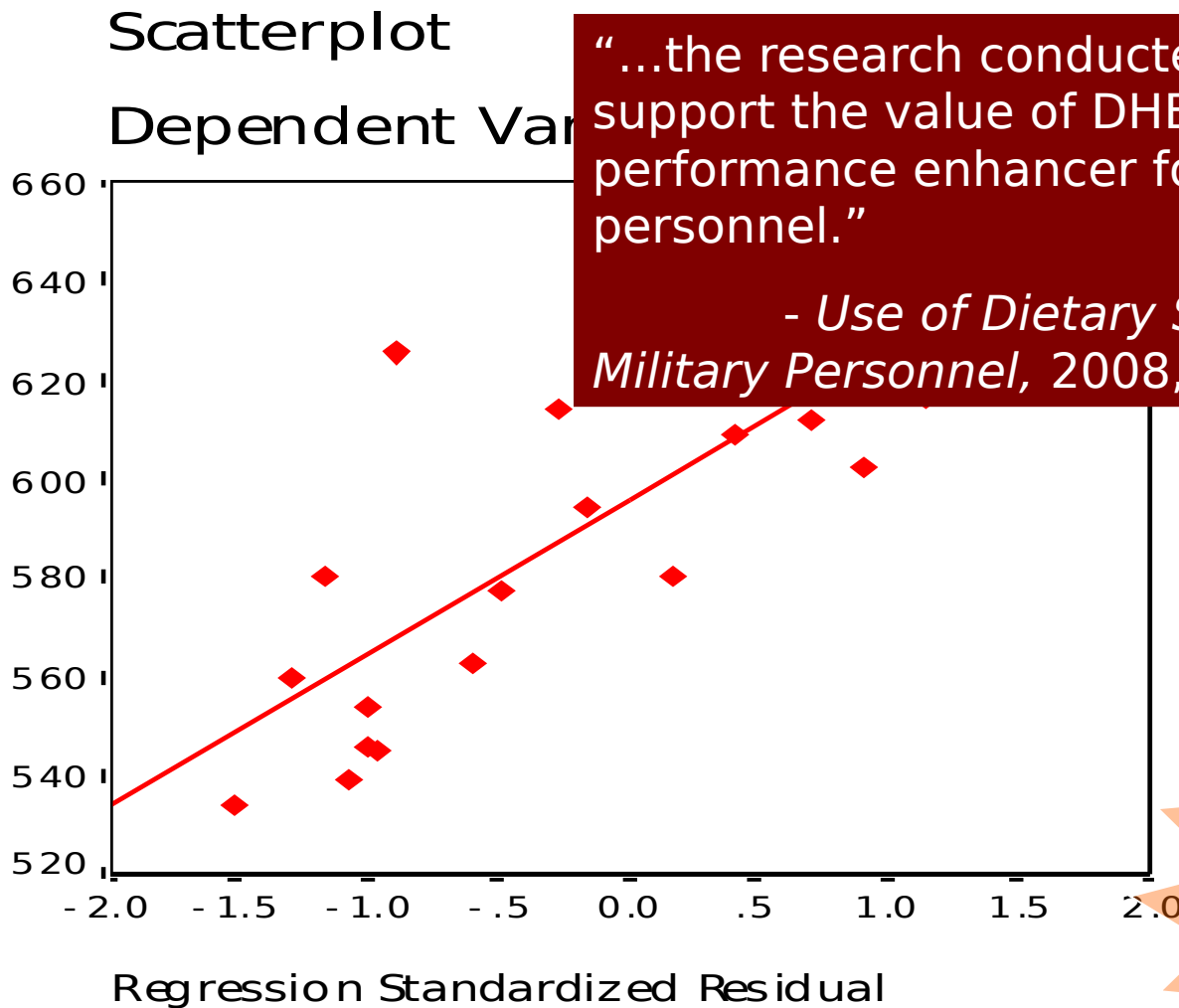
# Epigenetic Regulation

## “Moth-balled gene”



**Diet-based deacetylase inhibitors like bacterial fermentation of carbohydrate within the gastrointestinal tract, ketones (butyrate, valproic acid), ketogenic diet?**

# A side point...



“...the research conducted does not support the value of DHEA as a performance enhancer for military personnel.”

- *Use of Dietary Supplements by Military Personnel, 2008, IOM*

$Rsq = 0.6936$

# Nutrigenetics: yet more speculation

- **The prevalence of folate-remedial MTHFR enzyme variants in humans.**

Marini N.J., Gin J, Ziegler J, Kehoe KH, David Ginzinger D., Gilbert D. and Rine J. *PNAS*, v.105(2): June 10, 2008

- Sampled 11 methylenetetrahydrofolate reductase (MTHFR) SNPs, from 564 individuals of diverse ethnicities
- “Multiple less-frequent alleles, in aggregate, might significantly contribute to metabolic dysfunction. Furthermore, vitamin remediation of mutant enzymes may be a common phenomenon in certain domains of proteins.”

- **Broccoli Consumption Interacts with GSTM1 to Perturb Oncogenic Signalling Pathways in the Prostate.**

Traka M, Gasper AV, Melchini A, Bacon JR, Needs PW, et al. (2008) *PLoS ONE* 3(7): e2568.

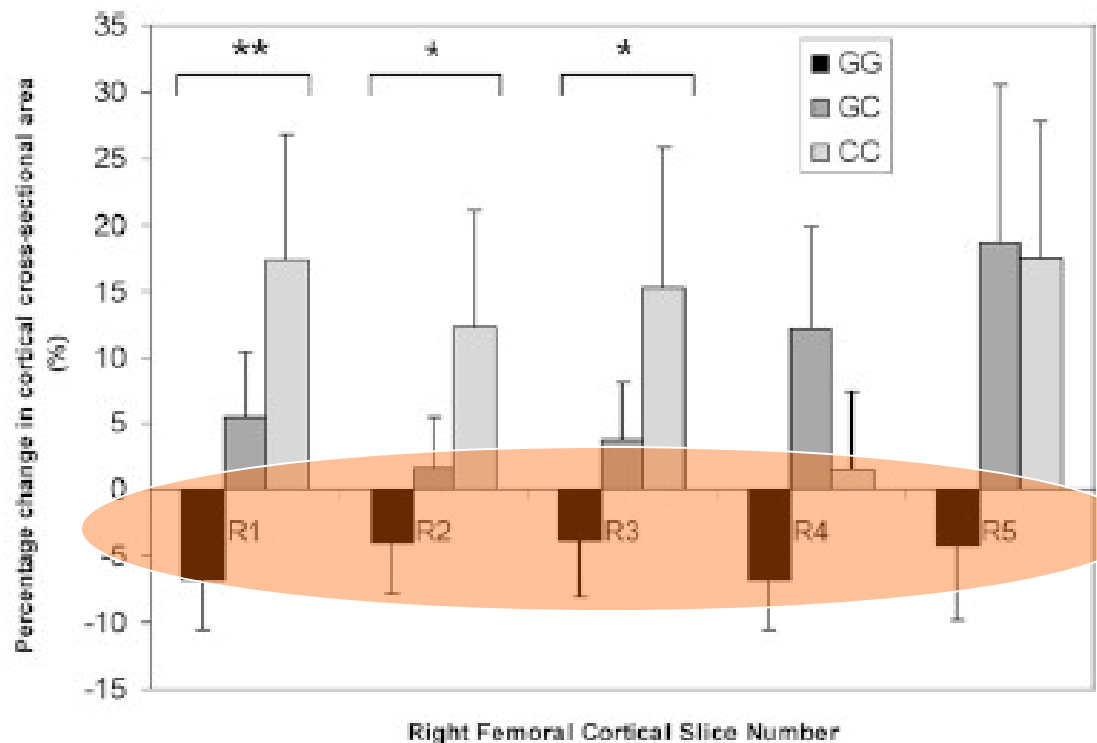
- **Genetic Variant in the Glucose Transporter Type 2 (GLUT 2) is Associated with Higher Intakes of Sugars in Two Distinct Populations.**

Ahmed El-Sohemy, A., Eny, K.M., Wolever, T., and Fontaine-Bisson, B. (2008) *Physiological Genomics* May 2008



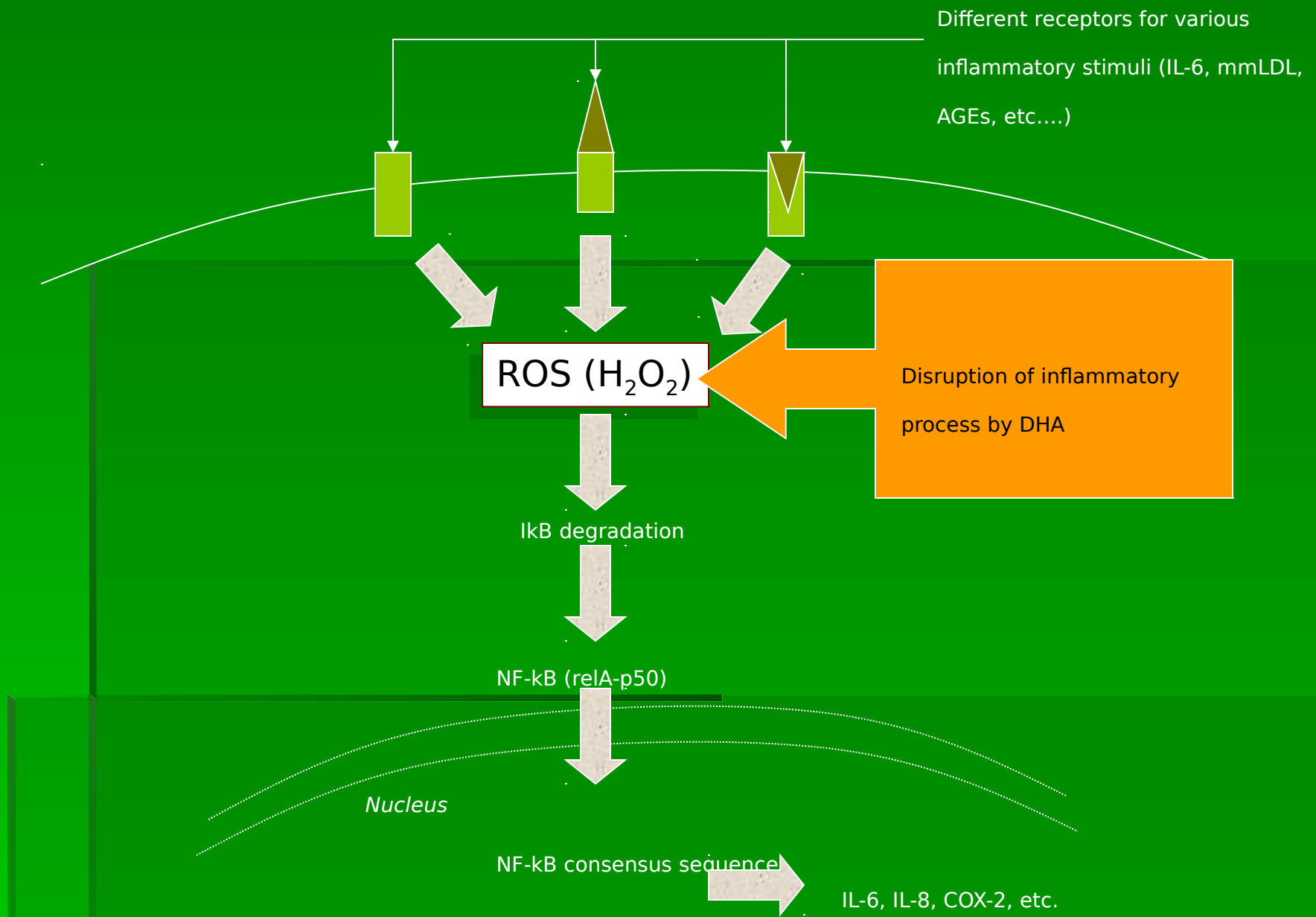
# IL-6 SNP and bone density

Fig. 1 Mean percentage change in right femoral cortical cross-sectional area in five slices taken at 50 mm intervals (*R1*/proximal to *R5*/distal) associated with a 10-week strenuous exercise training programme in 130 young healthy males genotyped for the -174 G>C IL-6 gene promoter polymorphism. \*\* $P = 0.027$  by ANOVA;  $P = 0.007$  for linear trend. \* $P < 0.05$  for linear trend; ANOVA NS



Wienberg equilibrium

- GG: 36%
- GC: 47%
- CC: 22.17%

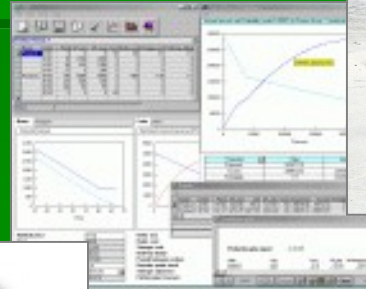
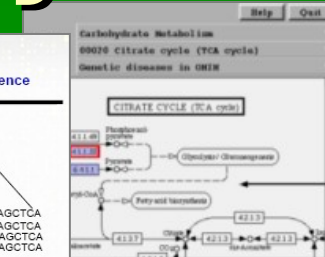
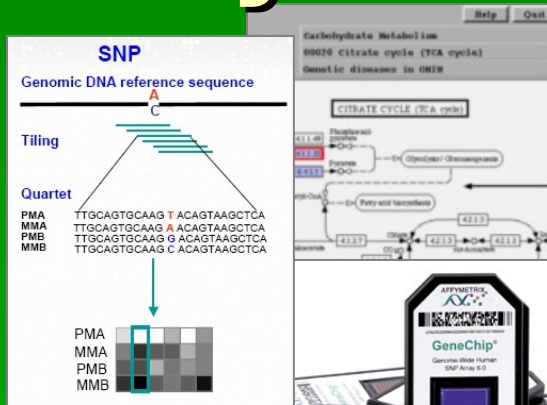


# Paradigm Shift

- As nutrigenomics is inherently PRO-active, the challenge is going to be getting from:
  - Description: this creature eats **x**, then **y** (sometimes) happens...or not
  - Prediction: therefore, if creature eats **x**, then **y** will/will not have a better chance of happening
  - Prescription: if creature does not want **y**, create



# Beyond speculation



**your cell phone your wellphone! It's Easy, Fun and Free!**  
Wherever you're on-the-go to help you stay on your path to feeling good...

**Get reminders**  
Keep "forgetting" about your diet?  
Need a little extra nudge?  
Trying to stay on a routine?  
[Learn more](#)

**Get tips**  
Need weight loss suggestions?  
Tricks for keeping stress away?  
Motivation boosts?  
[Learn more](#)

**Log your progress**  
Shipped that desert?  
Just ran 3 miles?  
Want everyone to know?  
[Learn more](#)

**Find local resources**  
Looking for a spa nearby?  
In the mood to try yoga?  
Traveling out of town?  
[Learn more](#)

**Receive notifications**  
Want to keep up with friends?  
Hear about upcoming events?  
See who cheered you on?  
[Learn more](#)

**Update your journal**  
Resisted temptation today?  
Feeling energized?  
Struggling to find motivation?  
[Learn more](#)

**Get Wellalternatives**  
Out at your favorite restaurant?  
Want nutrition info on a menu item?  
Looking for a healthier alternative?  
[Learn more](#)

**Ready to make your cell phone your wellphone?**  
[Get started!](#)

**just text:  
"well"  
to 878787**

**Share:** [Facebook](#) [Twitter](#) [LinkedIn](#) [Google+](#)

The best way to predict the future  
is to create it.

- Abraham Lincoln

# Oh, yeah...

- **Practical Issues**

- Novel nutrient-gene interactions
- New diagnostic tests for responses to diets and new biomarkers like mRNA for stress (oxidative or otherwise) that can be used to detect biopotency/applicability
- Identifying specific populations with special needs
- Improving the definitions and methodologies related to dietary assessment
- Providing information to make “food +”

- **Ethical Issues**

- Consent
- GINA – may mean something different to military (i.e. 2001 Burlington Northern Santa Fe lawsuit where the company tested workers with carpal tunnel syndrome for genetic predisposition; athletes prevented from competing if they have hypertrophic cardiomyopathy (HCM) – Chicago Bulls and Eddy Curry.
- Confidentiality
- Solidarity (same species, different creatures)
- Knowing what’s coming (AD risk for example)
- Access: right now, the rich can afford this and may drive it forward – but if there’s really a there there, shouldn’t it be made available to those who need it most: the disadvantaged, the diseased, and the defenders?

- **Methodological Issues**

- Study design limitations
- Need to incorporate epigenetics
- SNP identification and haplotyping
- Dietary intake assessment
- Better biomarkers
- Demonstrate analytical AND clinical validity
- Clinical utility



# Thanks

Thanks due to Ann Rasmussen (Yale),  
Gary Hazlett (Cody Woodward LLC),  
and Andy Morgan (Yale)

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